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## **EVASION STRATEGY OF HUMAN CYTOMEGALOVIRUS FROM THE ANTIVIRAL ACTIVITIES OF APOBEC3G**

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The apolipoprotein B editing enzyme catalytic subunit 3 (APOBEC3) is a family of DNA cytosine deaminases that mutate and inactivate viral genomes by single-strand DNA editing, thus providing an innate immune response against a wide range of DNA and RNA viruses. In particular, APOBEC3A (A3A), a member of the APOBEC3 family, is induced by human cytomegalovirus (HCMV) in decidual tissues where it efficiently restricts HCMV replication, thereby acting as an intrinsic innate immune effector at the maternal-fetal interface. However, the widespread incidence of congenital HCMV infection implies that HCMV has evolved to counteract APOBEC3-induced mutagenesis through mechanisms that still remain to be fully established. Here, we have assessed gene expression and deaminase activity of various APOBEC3 gene family members in HCMV-infected primary human foreskin fibroblasts (HFFs). Specifically, we show that APOBEC3G (A3G) and to a lesser degree A3F, but not A3A, gene products are upregulated in HCMV-infected HFFs. We also show that HCMV mediated induction of A3G expression is mediated by interferon- $\beta$  (IFN- $\beta$ ), which is produced early during HCMV infection. However, knockdown or overexpression of A3G does not affect HCMV replication, indicating that A3G is not a restriction factor for HCMV. Finally, through a bioinformatics approach, we show that HCMV has evolved mutational robustness against IFN- $\beta$  by limiting the presence of A3G hotspots in essential open reading frames (ORFs) of its genome. Overall, our findings uncover a novel immune evasion strategy by HCMV with profound implications for HCMV infections

## **CHARACTERIZATION OF IN VITRO ZIKV RESISTANCE TO SOFOSBUVIR, A LICENSED HIGH- GENETIC BARRIER HCV RNA-POLYMERASE INHIBITOR**

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The increased incidence of congenital malformation and neurological disorders associated to Zika virus (ZIKV) led the World Health Organization to declare ZIKV an international public health emergency. While recent efforts have primarily focused on vaccine development, treatments for infected individuals are urgently needed. Given the homology between ZIKV and HCV polymerase enzymes, sofosbuvir, a high-genetic barrier nucleotide analog RNA- polymerase inhibitor approved by FDA for the treatment of HCV infection is being considered as an anti-ZIKV agent. Indeed, the anti-ZIKV activity of sofosbuvir has been showed in vitro with cell-based assay and in animal models. However, sofosbuvir drug genetic barrier has been not yet evaluated with ZIKV.

In this study, the HP/F/2013 ZIKV strain was propagated in the Huh-7 cell line with increasing concentrations of sofosbuvir. Viral clones replicating at each drug increment step were collected and sequenced to detect emergent mutations in the polymerase (NS5) region. At sofosbuvir concentration of 5, 10 and 20  $\mu$ M, no NS5 changes were observed while the virus breakthrough time grew with increasing drug concentration (5, 15, 22 and 51 days, respectively). At 40  $\mu$ M, we detected the V607I mutation, located in the highly conserved NS5 motif B (SGxxxT) expected to interact with sofosbuvir. However, no shift in sofosbuvir was observed with the mutant virus with respect to wild type through ELISA cell based assay. Thus, the V607I mutation warrants further studies.